Response Properties and Organization of Nociceptive Neurons in Area 1 of Monkey Primary Somatosensory Cortex

DAN R. KENSHALO,[1,2] KOICHI IWATA,[3] MAURICE SHOLAS,[4] AND DAVID A. THOMAS
[1]*Pain and Neurosensory Mechanisms Branch, National Institute of Dental Research and* [2]*The Center for Scientific Review, National Institutes of Health, Bethesda, Maryland 20892;* [3]*Department of Physiology, Nihon University School of Dentistry, Tokyo 101, Japan; and* [4]*Program in Neuroscience, Division of Medical Sciences, Harvard Medical School, Boston, Massachusetts 20115*

Received 12 March 1998; accepted in final form 17 April 2000

Kenshalo, Dan R., Koichi Iwata, Maurice Sholas, and David A. Thomas. Response properties and organization of nociceptive neurons in area 1 of monkey primary somatosensory cortex. *J Neurophysiol* 84: 719–729, 2000. The organization and response properties of nociceptive neurons in area 1 of the primary somatosensory cortex (SI) of anesthetized monkeys were examined. The receptive fields of nociceptive neurons were classified as either wide-dynamic-range (WDR) neurons that were preferentially responsive to noxious mechanical stimulation, or nociceptive specific (NS) that were responsive to only noxious stimuli. The cortical locations and the responses of the two classes of neurons were compared. An examination of the neuronal stimulus-response functions obtained during noxious thermal stimulation of the glabrous skin of the foot or the hand indicated that WDR neurons exhibited significantly greater sensitivity to noxious thermal stimuli than did NS neurons. The receptive fields of WDR neurons were significantly larger than the receptive fields of NS neurons. Nociceptive SI neurons were somatotopically organized. Nociceptive neurons with receptive fields on the foot were located more medial in area 1 of SI than those with receptive fields on the hand. In the foot representation, the recording sites of nociceptive neurons were near the boundary between areas 3b and 1, whereas in the hand area, there was a tendency for them to be located more caudal in area 1. The majority of nociceptive neurons were located in the middle layers (III and IV) of area 1. The fact that nociceptive neurons were not evenly distributed across the layers of area 1 suggested that columns of nociceptive neurons probably do not exist in the somatosensory cortex. In electrode tracks where nociceptive neurons were found, approximately half of all subsequently isolated neurons were also classified as nociceptive. Low-threshold mechanoreceptive (LTM) neurons were intermingled with nociceptive neurons. Both WDR and NS neurons were found in close proximity to one another. In instances where the receptive field shifted, subsequently isolated cells were also classified as nociceptive. These data suggest that nociceptive neurons in area 1 of SI are organized in vertically orientated aggregations or clusters in layers III and IV.

INTRODUCTION

Although it is generally recognized that the primary somatosensory cortex (SI) plays a role in the processing of innocuous tactile information, its role in pain sensation remains unclear. Head and Holmes (Head 1920; Head and Holmes 1911; Holmes 1927) suggested that the cerebral cortex did not play an essential role in pain sensation. This conclusion was based on observations that patients with parietal lobe lesions rarely exhibited a permanent loss of pain sensation. However, they also noted that cerebral lesions could result in a temporary loss of pain sensation (Head 1920). They viewed the cortex as controlling information from the lateral thalamus, where nociceptive information purportedly entered conscious sensation. The results of Penfield and colleagues (Penfield and Boldry 1937; Penfield and Jasper 1954) supported the conclusions of Head, given that electrical stimulation of the somatosensory cortex rarely elicited reports of pain in patients undergoing ablative procedures for epilepsy (for review, see Kenshalo and Willis 1991).

By contrast, other lines of evidence suggested SI might be involved in pain sensation. In a number of studies, ablation or injury of SI produced impairments in humans' sensitivity to cutaneous pain (Dejerine and Mouzon 1915; Foerster 1927; Marshall 1951; Russell 1945). Restricted SI lesions produced deficits in monkeys' responses to pin prick stimuli (Peele 1944). Similarly, Brinkman et al. (1985) found that transient cooling of somatosensory cortex in awake behaving monkeys reduced the responsiveness of the animal to pin prick stimuli. Bilateral lesions of cytoarchitectonic areas 3a, 3b, 1 and 2, which comprise SI, produced long-lasting deficits in the monkeys' detection and discrimination of noxious thermal stimulation (Kenshalo et al. 1989).

Single unit recordings in area 1 demonstrate neurons exist that encode the intensity of noxious thermal stimulation of the skin (Chudler et al. 1990; Kenshalo and Isensee 1983; Kenshalo et al. 1988). In addition, stimulation of the tooth-pulp, at sufficient intensity to produce pain in humans, activates neurons in the face representation of SI (Anderson et al. 1977; Biedenbach et al. 1979; Iwata et al. 1987, 1990; Matsumoto et al. 1987; Roos et al. 1983a,b). Manipulations that alter humans' intensity of pain sensation, such as interstimulus interval, produce concomitant changes in the discharge of nociceptive SI neurons (Chudler et al. 1990). Furthermore, the discharge frequency of wide-dynamic-range (WDR) neurons in area 1 of SI correlates with the ability of monkeys to detect noxious thermal stimulation (Kenshalo et al. 1988). These results suggest that nociceptive cortical neurons in area 1 of the primary somatosensory cortex of primates participate in the

Address for reprint requests: D. R. Kenshalo, Center for Scientific Review, Rm. 5182, MSC7844, 6701 Rockledge Dr., Bethesda, MD 20814-9692 (E-mail: Kenshald@csr.nih.gov).

The costs of publication of this article were defrayed in part by the payment of page charges. The article must therefore be hereby marked "*advertisement*" in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

encoding process through which monkeys perceive the intensity of noxious thermal stimulation. By contrast Tommerdahl et al. (1996), based on optical imaging methods that registered changes in blood flow, concluded that area 3a ". . . plays the most prominent role in the processing of information from distal forelimb skin receptors sensitive to elevations in skin temperature perceived as painful" (p. 2666).

Although evidence of the involvement of SI in pain sensation has increased, little is known concerning the distribution and laminar organization of nociceptive neurons in the primate. In the present study, these two features of cortical organization were examined. In addition, the responses to noxious thermal stimulation of WDR and nociceptive specific neurons are compared.

METHODS

Experiments were performed in 17 young adult macaque monkeys (*Macaca fascicularis*). The animals were sedated with ketamine (10 mg/kg im), an intravenous catheter was introduced, and alpha-chloralose (80 mg/kg) was injected intravenously to maintain anesthesia. A stable level of anesthesia, as judged by meiosis and areflexia, was produced by a constant intravenous infusion of pentobarbital sodium ($4–5\ mg \cdot kg^{-1} \cdot h^{-1}$). This anesthetic regimen has been used in numerous studies on the spinothalamic tract neurons, thalamic and nociceptive cortical neurons (Chudler et al. 1990; Kenshalo and Isensee 1983; Kenshalo et al. 1979, 1983; D. K. Douglass, M. Sholas, D. A. Thomas, R. Dubner, and D. R. Kenshalo, unpublished observations). During recording sessions the animals were paralyzed, artificially ventilated, and their end-tidal CO_2 concentration kept between 3.5 and 4.5%. The animals were never given pancuronium bromide prior to the start of the recording session. Body temperature was regulated near 37.5°C by a feedback-controlled electric blanket.

The animal's head was placed in a stereotaxic frame and a craniotomy exposed the dura overlying SI. The dura was reflected and a Plexiglas cylinder cemented to the surrounding skull. The cylinder was then filled with warm (37.5°C) mineral oil. Another piece of Plexiglas, attached to a micromanipulator, was positioned above the cylinder and served to close the chamber and to prevent cortical pulsations. A tungsten microelectrode (2–9 megohms at 1 kHz) was used to search SI for cellular activity. As the microelectrode advanced through the cortex, tapping on the appropriate region of the body evoked cellular activity.

When action potentials were isolated from surrounding activity, the receptive field of the neuron was tested with a standard series of mechanical stimuli. Mechanical stimuli included brushing the receptive field with a cotton swab (light touch), application of a large arterial clip (pressure), and application of a small arterial clip (pinch). In addition, each neuron was tested for responses from subcutaneous receptors by pinching a fold of skin, which included deep tissue. The large arterial clip produced a sensation of pressure when applied to human skin and exerted a force of 144 g/mm^2; the small arterial clip produced a distinct sensation of pain and exerted a force of 538 g/mm^2. If the response was larger with the addition of deep tissue, then it was assumed that the neuron received a convergent input from deep receptors. Low-threshold, mechanoreceptive (LTM) cells responded with the highest discharge frequencies to hair movement, light touch, or pressure, and did not increase their firing frequency with increases in stimulus intensity in the noxious range. WDR neurons responded to hair movement, light touch, and pressure, but a pinch stimulus produced the highest discharge frequency. Nociceptive-specific (NS) neurons responded to pressure and pinch stimuli, but did not respond to hair movement or light touch of the skin. This classification scheme or variations of it has been used to describe nociceptive neurons in the spinal (Willis 1985) and medullary dorsal horns (Dubner and Bennett 1983). It has also been used to classify nociceptive neurons in ventral posterior lateral nucleus caudalis and ventral posterior medial nucleus of the thalamus (Bushnell and Duncan 1987; Kenshalo et al. 1980), the somatosensory cortex of anesthetized monkey and rat (Chudler et al. 1990; Iwata et al. 1990; Kenshalo and Isensee 1983; Lamour et al. 1983a,b) and the SI cortex of awake, trained monkeys (Kenshalo et al. 1988).

Neuronal activity was analyzed by a Bak window discriminator and fed to a dual beam oscilloscope. On one beam of the oscilloscope action potentials that triggered the window discriminator were monitored for spike amplitude and duration. Additionally, action potentials were fed to an analog delay module. Pulses from the trigger level of the window discriminator were used to initiate a sweep of the oscilloscope and pulses from the window discriminator were fed to the z-axis intensification of the oscilloscope. This configuration allowed action potentials that triggered the window discriminator to be displayed on the second beam of the oscilloscope on a faster time base and checked for constancy of spike height and waveform. Given the configuration of the window discriminator system, it is highly unlikely that units recorded at subsequent points represent the discharge from the same neuron. In cases where subsequently isolated receptive fields were identical, the action potential shapes were required to be sufficiently different to clearly separate the two neurons. In addition, the action potential shape and waveform must have changed abruptly for the subsequently isolated neuron to be considered a different cell. The output of the discriminator was fed to a computer for on-line compilation of peristimulus time histograms during the series of mechanical stimuli.

The receptive fields of neurons were mapped using low threshold, mechanical stimuli and were drawn on a figure of the monkey's hand or foot. WDR and NS neurons were then tested for responses to noxious thermal stimuli with a Peltier thermal stimulator (Kenshalo and Bergen 1975). The surface area of the thermal stimulator was 18 cm^2, but only a sufficient area of the stimulator was placed on the skin to cover the majority of the receptive field. The skin was adapted to 35°C for 3 min and then heated to final temperatures of 43, 45, 47, and 50°C. The duration of each thermal stimulus was 30 s. A 3-min re-adaptation period was interposed between each temperature change, and the rate of change was 2°C/s. The influence of sensitization of nociceptive afferents was avoided because we only compared the stimulus-response functions of the first or second nociceptive neuron studied on each limb of the monkey. The nonspecific influences (i.e., changes in arousal or blood pressure) of noxious thermal stimuli were assessed by delivering a 50°C noxious thermal stimulus outside the area of the receptive field, usually on the opposite limb. The contribution of slowly adapting mechanoreceptors, warm receptors, and cold receptors to the noxious heat response was determined by cooling the receptive field from 35 to 30°C. None of the nociceptive cortical neurons responded to cooling of the receptive field. In six experiments after the initial receptive field was mapped and the responses to mechanical stimulation and thermal stimulation were recorded, capsaicin (50 μg in 20 μl Tween) was injected intradermally with a tuberculin syringe into the most mechanically sensitive portion of the receptive field.

Peak frequency, the greatest number of impulses occurring during a 1 s bin, was used to measure neuronal responsiveness and to construct stimulus-response functions. In past studies, this metric produced the highest correlation between neuronal activity and sensation in the awake behaving monkey (Chudler et al. 1990; Dubner et al. 1989; Kenshalo et al. 1988; Maixner et al. 1989). A repeated measures analysis of variance (ANOVA) was used to assess the overall effect of stimulus temperature on neuronal activity. A Duncan's multiple range test (Winer 1971) was used as a post hoc test to determine significant differences in neuronal discharge. The thermal threshold was defined as the lowest stimulus intensity necessary to produce a statistical increase in discharge frequency. To determine the thermal threshold, a paired *t*-test was performed on the number of

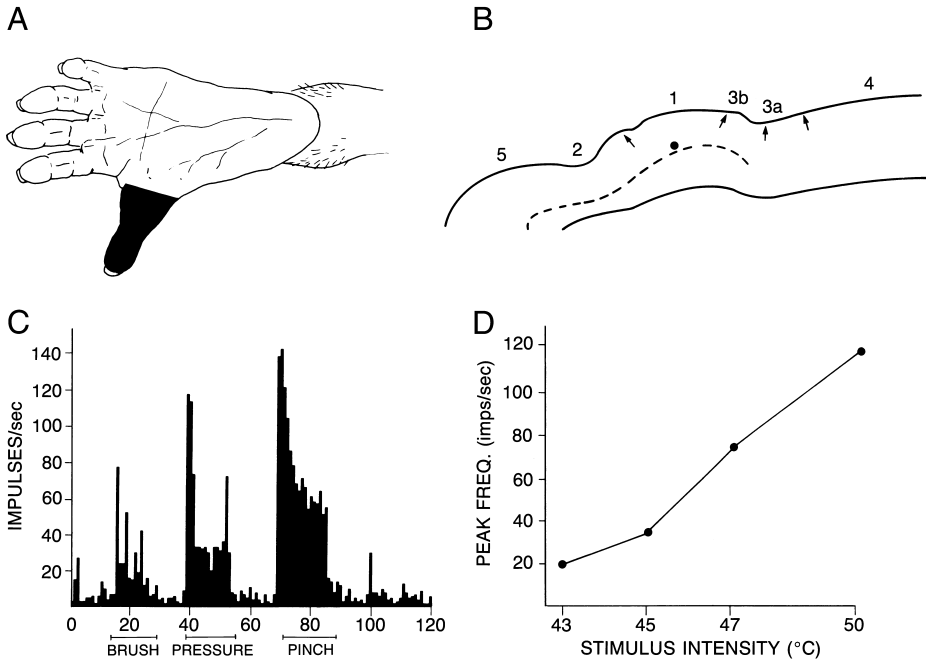

FIG. 1. Response properties of a wide-dynamic-range (WDR) cortical neuron. The low-threshold receptive field was located on the glabrous skin of the hallux, as indicated by the dark area. The recording site was located in area 1, as shown in *B*. The arrows indicate the approximate location of cytoarchitectonic borders and the dashed line represents the middle of layer 4. The peristimulus time histogram in *C* shows the graded responses to brushing, pressure, and pinching the receptive field. Stimulus-response function to an ascending series of noxious thermal stimuli delivered to the receptive field is shown in *D*. In this and all subsequent peristimulus time histograms the binwidth was 1 s.

spikes in each bin 10 s prior to stimulation and the number of spikes in each bin 10 s during noxious thermal stimulus.

In 61 electrode tracks, after an initial nociceptive neuron was isolated, subsequently isolated cells in the electrode tract were characterized and their responses to the standard series of mechanical and thermal stimuli were determined. Only neurons with action potentials of different shapes were categorized to ensure that subsequently isolated units recorded along the electrode tract represented different cells. When neurons were no longer isolated, the location of the electrode was marked with a lesion (10–20 uA for 10 s), the electrode was retracted to the recording site of the first nociceptive neuron and lesioned. Given the distance between the two lesions, it was possible to determine the location of each isolated neuron in the electrode track. At the conclusion of the experiment, the animal was perfused with 10% buffered formalin and the tissue was postfixed for several days. Frozen sections (50 microns thick) were cut in a parasagittal plane and stained with cresyl violet. Sections with lesions were traced and the appropriate cytoarchitectonic borders were labeled according to Jones and Burton (1976) and Jones et al. (1978).

RESULTS

In 17 monkeys, a total of 171 neurons were encountered in SI that responded with a progressive increase in discharge frequency to graded intensities of noxious thermal stimulation or to an intradermal injection of capsaicin. All of the neurons excited by noxious thermal stimulation and tested with an intradermal injection of capsaicin responded. The population of nociceptive neurons included 136 WDR and 35 NS neurons. All of the receptive fields were located on the glabrous skin of the hand or the foot. Each neuron responsive to noxious thermal stimulation was tested for responses to innocuous cold stimuli; none responded. In addition, each neuron was tested for responses to deep tissue stimulation. None of the nociceptive neurons increased their discharge frequency when deep tissue was stimulated.

The population used for quantitative analysis of the responses to noxious thermal stimulation included 19 WDR and 13 NS neurons. The neurons used in the quantitative analysis were chosen because they were the first or second isolated cells and their receptive fields were not damaged by prior noxious thermal stimulation. Repeated noxious thermal stimuli are known to sensitize the responses and lower the threshold of nociceptors (Campbell et al. 1979; Croze et al. 1976), spinothalamic tract neurons (Kenshalo et al. 1979), and nociceptive neurons in the thalamus and cortex (Kenshalo et al. 1980, 1983; Lamour et al. 1983a). In addition, repeated noxious stimuli are also known to enlarge the receptive fields of dorsal horn neurons (Laird and Cervero 1989) and nociceptive neurons in SI (D. K. Douglass, M. Sholas, D. A. Thomas, R. Dubner, and D. R. Kenshalo, unpublished observations). Thus the responses of the nociceptive neurons in the present study have not been confounded by prior noxious thermal stimulation.

The characteristics of a WDR neuron are illustrated in Fig. 1. The receptive field, determined by mechanical stimulation of the skin, was confined to the glabrous skin of the hallux. A common characteristic of receptive fields of WDR neurons was an area of the skin that was sensitive to low-threshold mechanical stimulation (Fig. 1*A*). The recording site was marked with an electrolytic lesion and was located in layer 4 of area 1 (Fig. 1*B*). A peristimulus time histogram of the responses to the series of mechanical stimuli is shown in Fig. 1*C*. Brushing the receptive field produced an increase in the discharge frequency of the cell, but the largest response was obtained after application of a small arterial clip (pinch). The stimulus-response function from graded intensities of noxious thermal stimulation is shown in Fig. 1*D*. A monotonic relationship was found between the peak discharge frequency and the intensity of noxious thermal stimulation.

An example of an NS neuron is shown in Fig. 2. The receptive field was confined to the distal phalanges of the index finger (Fig. 2*A*). The recording site was located in layer 3 of area 1 (Fig. 2*B*). Brushing the receptive field did not produce a response from the neuron (Fig. 2*C*). More intense mechanical stimuli, such as pressure and pinch, produced graded increases

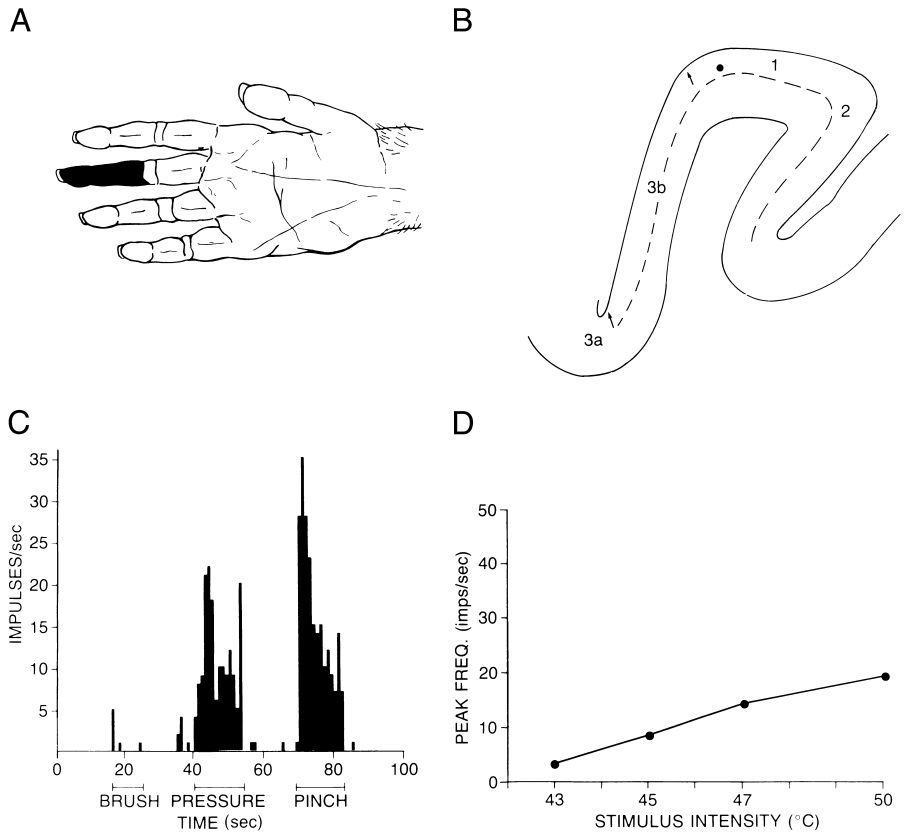

FIG. 2. Response properties of a nociceptive specific (NS) neuron. The receptive field is shown in *A* and the location of the recording site in *B*. The peristimulus time histogram in *C* shows the absence of a response to brushing and a graded response to a pressure and a pinch stimulus. The graph in *D* shows the stimulus-response function to a graded series of noxious thermal stimuli.

in discharge frequency. Noxious thermal stimuli also evoked an increase in activity of the cell, which graded with stimulus intensity (Fig. 2*D*).

Responses of WDR and NS neurons to noxious thermal stimulation

Averaged peristimulus time histograms of the responses of 19 WDR and 13 NS neurons to an ascending series of noxious thermal stimuli are shown in Fig. 3. Both populations of WDR and NS neurons encoded the intensity of noxious thermal stimuli. However, a number of differences were found in the response characteristics of WDR and NS neurons. Evident from this figure is the higher spontaneous discharge rate of WDR neurons compared with NS neurons. The average spontaneous activity of WDR neurons was 12.7 ± 2.9 (SE) impulses/s prior to noxious thermal stimulation. The average spontaneous activity of NS neurons was 2.2 ± 0.8 impulses/s. The difference in spontaneous activity between WDR and NS neurons was statistically significant (*t*-test; $P < 0.01$). The thermal threshold, the lowest temperature that increased neuronal discharge rate, was determined for each WDR and for each NS neuron. The average thresholds were 45.4 ± 0.4°C for WDR neurons and 46.3 ± 0.6°C for NS neurons. The difference in thermal thresholds between WDR neurons and NS neurons was statistically significant (*t*-test; $P < 0.05$).

Individual stimulus-response functions for 19 WDR and 13 NS neurons are shown in Fig. 4, *A* and *B*. The neuronal responses for most of the WDR and NS neurons increased in a monotonic fashion throughout the noxious stimulus range. Figure 4*C* shows the average peak response of these neurons as a function of stimulus temperature. Both WDR and NS neurons increased their discharge to noxious heat stimulation in a graded manner. An ANOVA performed on the peak discharge frequency determined that there was a statistically significant difference between WDR and NS neurons [$F(1,29) = 10.6$; $P < 0.01$]. The intensity of noxious thermal stimulation produced a statistically significant increase in neuronal discharge [$F(3,87) = 39.5$; $P < 0.01$]. The main effect of neuron class and the intensity of noxious thermal stimulation did not produce a significant interaction [$F(3,87) = 1.69$; $P > 0.05$], which indicates that the slope of the stimulus-response function obtained from WDR neurons was parallel to that obtained from NS neurons. The discharge rates of WDR neurons were significantly greater than the discharge rates of NS neurons for each intensity of noxious thermal stimulation (Duncan's multiple range test; $P < 0.01$). WDR neurons exhibited significant differences in the peak neuronal discharge between each intensity of the noxious thermal stimulus (Duncan's multiple range test; $P < 0.01$). In contrast, NS neurons only exhibited significant differences in peak neuronal discharge between thermal stimuli of 43 and 50°C (Duncan's multiple range test; $P < 0.01$).

Organization of nociceptive cortical neurons

We attempted to determine the proportion of WDR and NS neurons to LTM neurons in areas of the cortex that contained nociceptive neurons. We estimate that a nociceptive neuron is isolated in about one of every seven electrode tracks. If one were to eliminate instances where nociceptive neurons were found but not isolated, we estimate that nociceptive neurons are found in about one of every five electrode tracks. In 61 electrode penetrations made through area 1, once an initial

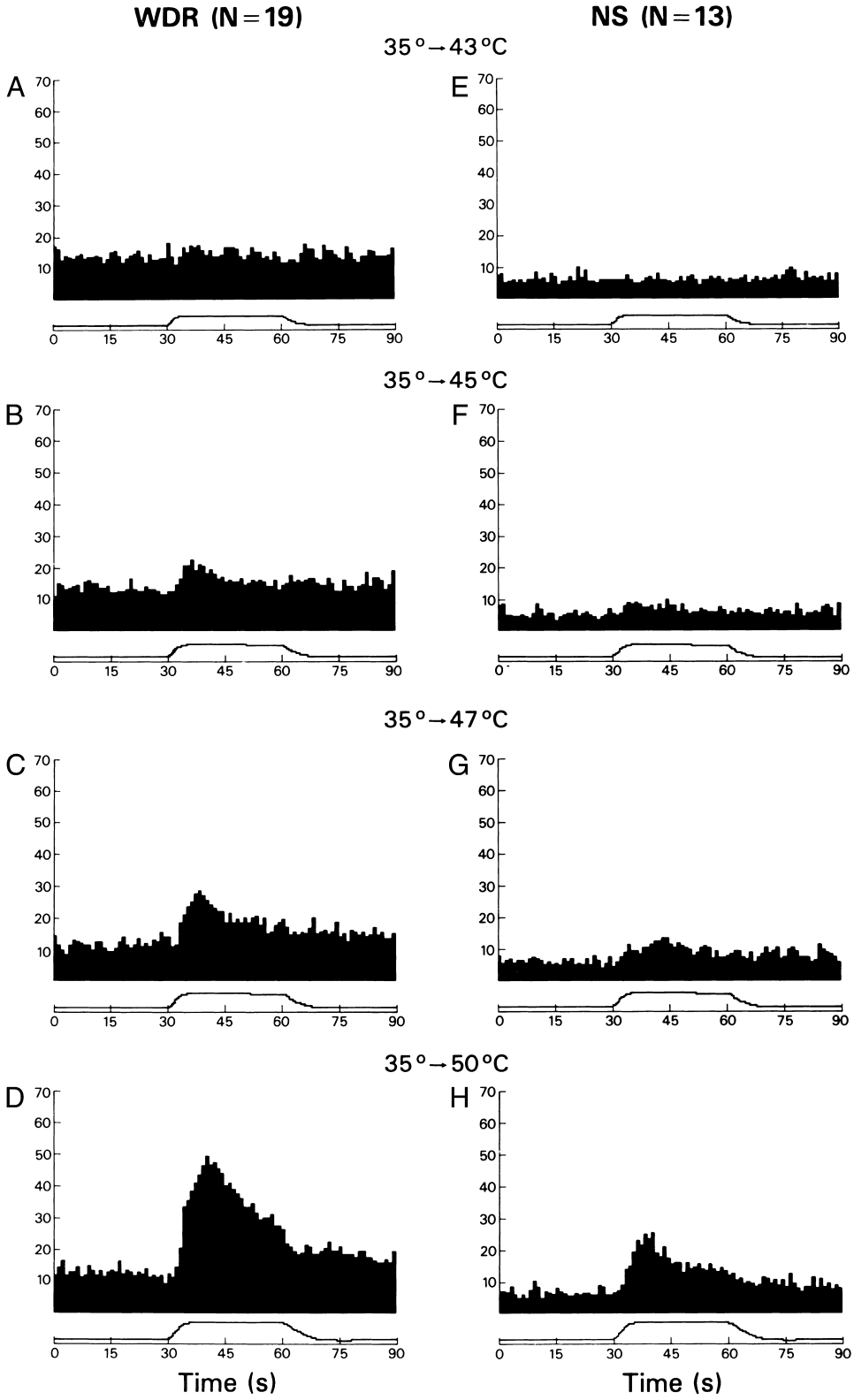

FIG. 3. Averaged peristimulus time histograms of the responses of 19 WDR and 13 NS neurons to an ascending series of noxious thermal stimuli. The histograms are the average of one trial from each neuron. The line beneath the histogram and above the abscissa indicates the time course of the noxious thermal stimulus.

nociceptive neuron was identified, the receptive fields of all subsequently isolated cells in the tract were characterized. After an initial nociceptive neuron was found, a total of 171 nociceptive (136 WDR and 35 NS) and 224 LTM neurons were isolated. This experiment yielded an average of 2.8 (range 2–6) nociceptive and 3.3 (range 1–5) LTM neurons per electrode tract.

In 95% (58/61) of the tracks the receptive fields of the LTM

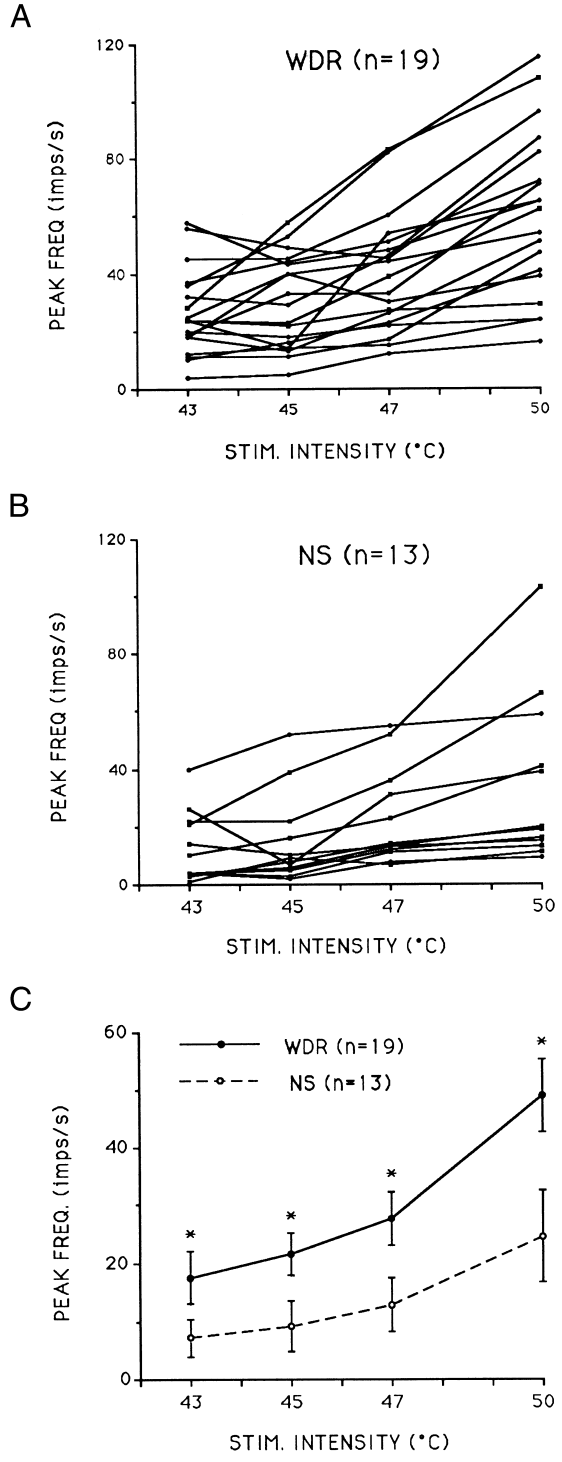

FIG. 4. Averaged stimulus-response functions of WDR and NS neurons to an ascending series of noxious thermal stimuli. In *A* and *B*, each point represents one trial from each neuron. *A*: the stimulus-response functions of the population of WDR neurons. *B*: the stimulus-response functions for the population of NS neurons. *C*: the average stimulus response functions for both classes of neurons. The asterisks indicate significant differences ($P < 0.01$, Duncan's multiple range test) between the discharge of WDR and NS neurons to identical noxious thermal stimuli. Error bars represent mean ± SE.

neurons overlapped with those of the nociceptive neurons. The three instances in which the receptive fields did not overlap were the result of only recording nociceptive neurons in the electrode track. An example of the organization of nociceptive and LTM neurons obtained from an electrode penetration through area 1 is shown in Fig. 5. The vertical line in the upper panel of Fig. 5 represents the microelectrode track through area 1. Circles on the track represent neurons isolated with WDR receptive fields and horizontal lines represent those with LTM receptive fields. The first nociceptive cell isolated was located in layer III and classified as a WDR neuron. The receptive field encompassed digits 4 and 5 on the foot (cell A). The next cell (B) was also classified as a WDR neuron and the receptive field location was similar to cell A. With further advancement of the electrode, the next two neurons (cells C and D) were classified as LTM neurons and the receptive fields shifted to digits 3, 4, and 5. The receptive fields of subsequently isolated cells (cell E) shifted to digits 4 and 5. The next three neurons (cells F, G, and H) all possessed similar receptive fields. However, cell E was classified as a WDR neuron, cell F as an LTM, cell G as a WDR neuron, and cell H as an LTM.

WDR and NS neurons are intermingled in a single tract through area 1. Figure 6 shows an initial WDR neuron with a receptive field located on the thumb and was located in layer 3 (cell A). With further advancement of the electrode, an NS neuron was isolated with a similar receptive field (cell B). The next two isolated neurons (cells C and D) also possessed similar receptive fields, but one was classified as a WDR and the other as an NS neuron. As the electrode entered layer IV two WDR neurons (E and F) were isolated, both with receptive fields located on digit 1. After the electrode entered layer V an LTM (G) neuron was encountered with a similar receptive field. No other neurons were isolated as the electrode was advanced through layer VI. These data illustrate that both WDR and NS neurons are intermingled with each other as well as LTM neurons.

Figure 7 illustrates an example of an electrode penetration

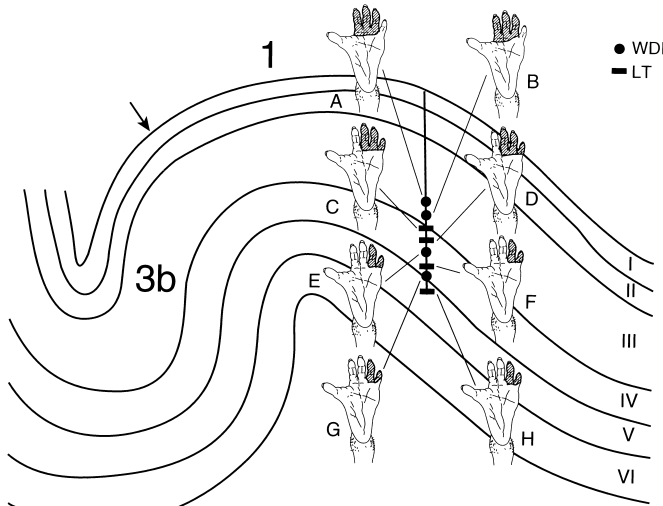

FIG. 5. Sequence of neurons encountered in an electrode penetration through the foot representation that contained WDR neurons. Upper panel is a parasagittal reconstruction of a section through the primary somatosensory cortex (SI). The vertical line in the upper panel shows an electrode penetration through the somatosensory cortex. Cells classified as low-threshold mechanoreceptive (LTMs) are represented by horizontal lines and WDR neurons by filled circles. All neurons classified as WDR or NS responded to noxious thermal stimuli applied to the receptive field. The letters along the electrode tract refer to the receptive field locations shown below.

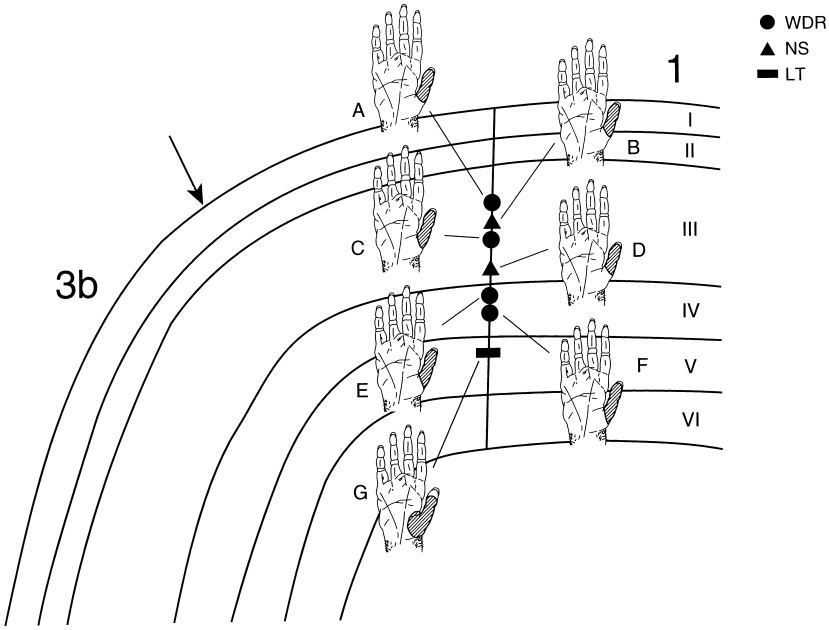

FIG. 6. Electrode penetration through the forelimb representation of SI. Cells classified as LTMs are represented by horizontal lines, WDR neurons by filled circles, and NS neurons by open circles. The letters along the electrode penetration refer to the receptive field locations shown below. All neurons classified as WDR or NS responded to noxious thermal stimuli applied to the receptive field.

that was slightly tangential to the surface of area 1. As the electrode penetrated the cortex, small movements produced striking shifts in the location of the receptive fields. Even though the receptive fields shifted with advancement of the electrode, WDR neurons were still encountered. These data suggest that within a cluster or aggregation of nociceptive neurons the receptive fields are not identical but may be partially shifted.

The locations of nociceptive neurons in area 1 of SI are shown in Fig. 8. A lateral view of the primate brain is illustrated in Fig. 8*A*. The locations of nociceptive neurons with receptive fields on the foot were more medial in SI cortex (Fig. 8*B*) than those nociceptive neurons with receptive fields on the hand (Fig. 8*C*). In the foot representation, the recording sites were near the boundary between areas 3b and 1, whereas in the hand area there was a tendency for the nociceptive neurons to be located more caudal in area 1. WDR neurons were distributed over a wider area of the cortex than were NS cells. The differential distributions of WDR and NS neurons were quantified by dividing the area of cortex that contained nociceptive neurons into equal quadrants. The number of lesions representing WDR and NS neurons were counted and a χ^2 test performed. The most rostral quadrant contained 16 WDR and 10 NS neurons, the second quadrant 18 WDR and 5 NS neurons, the third quadrant 18 WDR and 0 NS neurons, and the most caudal quadrant 8 WDR and 0 NS neurons. The χ^2 test revealed that the difference in distributions of WDR and NS neurons was highly significant ($\chi^2 = 12.08$; $P < 0.01$).

Nociceptive neurons were distributed in layers II to V. By far, layers III (32/75 or 43%) and IV (35/75 or 47%) contained the highest concentration of nociceptive neurons. Nociceptive neurons were not encountered in either layer I or VI. The

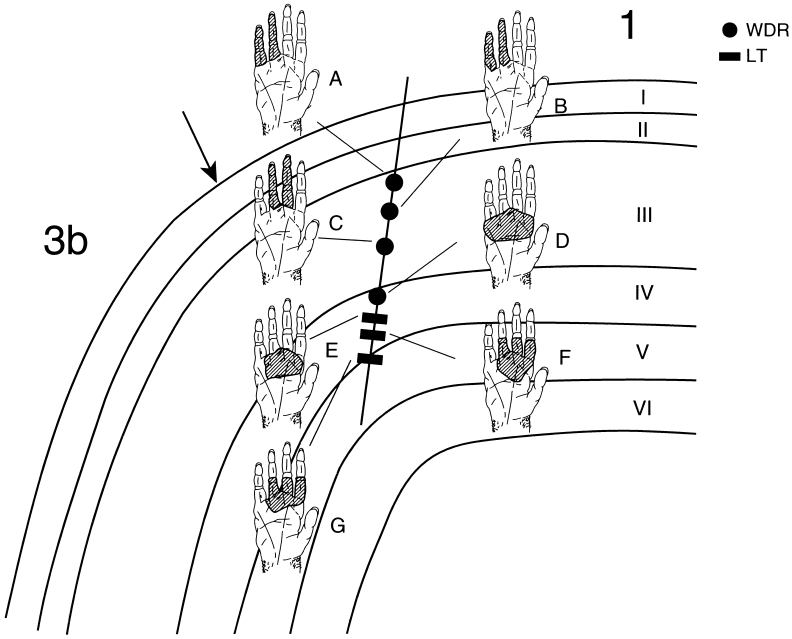

FIG. 7. Example of a slightly tangential electrode penetration through area 1 of SI. Small movements of the electrode produced striking shifts in the location of the receptive field. Even though the receptive field shifted dramatically, nociceptive neurons were isolated.

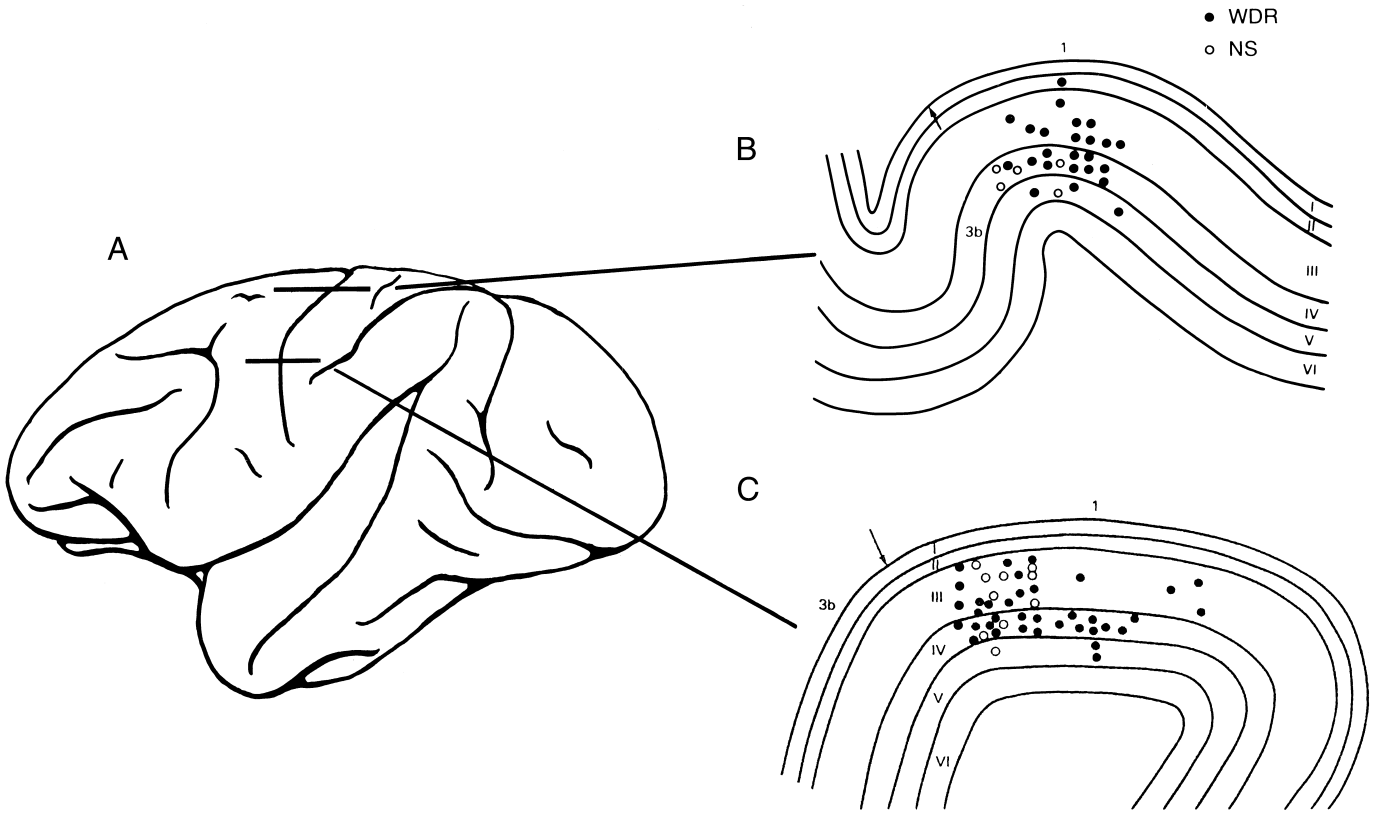

FIG. 8. *A*: a lateral view of the brain of a monkey. The lines indicate the approximate location of the sections shown in *B* and *C*. Cells with receptive fields located on the foot are shown in *B* and those with receptive fields on the hand were located more laterally as shown in *C*. WDR neurons are depicted by filled circles and NS neurons by open circles.

laminar distribution of WDR and NS neurons appeared to be similar. The highest concentration of the 60 WDR neurons was found in layer IV with 29 cells (41%) and layer III with 25 cells (41%). On rare occasions WDR neurons were found in layer V (5 cells, 8%) and layer II (1 cell, 2%). Similarly for 15 NS neurons, the highest concentration was also found in layer III with 7 cells (46%) and IV with 6 (40%) neurons. Infrequently NS neurons were found in layer V (2 cells, 7%). NS neurons were never encountered in layer VI.

DISCUSSION

The present data confirm and extend previous observations about neurons in area 1 of the primary somatosensory cortex of the monkey that encode the intensity of noxious mechanical and thermal stimulation (Chudler et al. 1990; Kenshalo and Isensee 1983; Kenshalo et al. 1988). The increase in the discharge rate of nociceptive cortical neurons is attributable to the activation of C-polymodal nociceptors (Beitel and Dubner 1976; Bessou and Perl 1969; Croze et al. 1976; Kumazawa and Perl 1977; LaMotte and Campbell 1978) and/or A-delta mechanoheat nociceptors (Beck et al. 1974; Campbell et al. 1979; Dubner et al. 1977; Georgopoulos 1976; Iggo and Ogawa 1971; Meyer and Campbell 1981).

The activity of cold receptors can be discounted from contributing to the increase in activity during noxious thermal stimulation of nociceptive cortical neurons. Cold receptors increase their discharge rate to skin cooling, whereas warm receptors decrease their discharge rate to skin cooling (Hensel 1973; Hensel and Kenshalo 1969; Kenshalo and Duclaux 1977). In the present experiments, the receptive field of each nociceptive cortical neuron was cooled; none altered their discharge. Given that none of the nociceptive neurons responded to innocuous cooling, it is highly unlikely that the responses to noxious thermal stimuli are the result of a paradoxical cold response. It has also been shown that slowly adapting mechanoreceptors do not respond to noxious thermal stimuli in the range of 43–50°C (Campbell et al. 1979). Thus the increase in activity of nociceptive SI neurons during noxious thermal stimulation is the result of an increase in activity of cutaneous nociceptors.

In the present study, the organization and response properties of NS and WDR neurons were compared. The stimulus-response functions indicated that WDR neurons were more sensitive to noxious thermal stimulation than NS cells. These data support the position that WDR neurons encode the intensity of noxious thermal stimulation more reliably than NS neurons. In addition, the cortical location of the two classes of neurons overlapped, but NS neurons were only found in the anterior half of the distribution of nociceptive neurons.

A major concern is the influence of anesthesia on the classification and receptive field size of nociceptive neurons. Some investigations have indicated that general anesthesia can reduce the rate of spontaneous activity, increase stimulus threshold, and reduce the receptive field sizes of low-threshold SI neurons (Armstrong-James and George 1988; Chapin et al. 1981; Duncan et al. 1982; Harding et al. 1979). The anesthetics used in the present study appear to affect minimally the size of the receptive field. In the face representation of SI, quantitative comparison of the receptive field areas of nociceptive neurons

in the anesthetized monkey (Chudler et al. 1990) and those in the awake, trained monkey (Kenshalo et al. 1988) were not statistically different. In addition, the proportion of WDR and NS neurons in the anesthetized and the unanesthetized monkey was similar. Thus it is reasonable to conclude that the classification of nociceptive neurons and receptive field size are marginally influenced by the anesthetic regimen used in the present study.

In a previous study the receptive fields of nociceptive neurons were classified according to the size of the receptive field (Kenshalo and Isensee 1983). Some neurons (80%) were found to have restricted receptive fields that only spanned one digit or limb of the monkey, while other neurons (20%) were found to have receptive fields that were activated by intense mechanical stimulation on any portion of the body. In the current study neurons with large receptive fields were not encountered. In the earlier study, if the neurons did not respond to 50°C, the receptive field was additionally heated to 53 and 55°C. In the current study temperatures above 50°C were not delivered to the receptive field. The only explanation we have for the discrepancy between the two studies is that the thermal thresholds of the neurons with large receptive fields may tend to be higher than those with smaller receptive fields.

Responses to noxious thermal stimulation

Both WDR and NS neurons are capable of encoding the intensity of noxious thermal stimulation. Each increase in stimulus intensity produced a statistically significant increase in the peak frequency of discharge in WDR neurons. For NS neurons, a statistically significant increase in the neuronal discharge was only found between noxious thermal stimuli of 43 and 50°C. These data suggest that the discharge of WDR cortical neurons provide more information concerning the intensity of painful stimulation than the discharge of NS neurons. However, it is unclear whether statistically significant differences in neuronal discharge are necessary to produce differences in the intensity of sensation. Information from NS neurons, therefore, cannot be discounted as participating in the encoding process of nociceptive stimulation. The average thermal threshold was 45.4°C for WDR and 46.3°C for NS neurons. The average thermal thresholds of WDR neurons are extremely close to the human threshold for faint pain 45.3°C reported by LaMotte and Campbell (1978). Thus the initiation of activity in WDR cortical neurons appears to provide a better approximation of the threshold for faint pain in humans than NS neurons.

The experience of pain can be classified into two components: a sensory-discriminative (e.g., quality, intensity, location, duration) component and a motivational-affective (arousal, unpleasantness, reflexive and integrated motor response) component (Hardy et al. 1952; Melzack and Casey 1968; Price and Dubner 1977). The discharge of WDR neurons appears more likely than NS cells to encode the intensity of noxious thermal stimulation. NS neurons, on the other hand, appear to be better suited to encode the temporal character of a noxious thermal stimulus. Our data suggest that WDR neurons are likely to be involved in encoding of the initial phasic response to noxious thermal stimulation, whereas NS neurons are better suited to signal noxious information of a longer duration. Similar results have been obtained using noxious mechanical stimulation for these two classes of neurons in the spinal cord of the rat (Cervero et al. 1988).

Organization of nociceptive SI neurons

The receptive fields of nociceptive neurons in area 1 of SI are somatotopically organized, similar to low-threshold mechanoreceptive neurons in the same region of cortex. The locations of nociceptive neurons with receptive fields on the foot were more medial than those with receptive fields on the hand. In the foot representation, the recording sites were near the boundary between areas 3b and l, whereas in the hand area, there was a tendency for the nociceptive neurons to be located more caudal in area 1. NS neurons tended to be located in the rostral portion of the distribution of nociceptive neurons. Both classes of neurons were distributed in layers II through V. Nociceptive neurons were not encountered in layer VI of SI.

Nociceptive neurons tended to be organized in aggregations within the SI. However, low-threshold neurons were found intermingled with nociceptive neurons. When small vertical movements of the electrode resulted in a shift in the location of the receptive fields, nociceptive neurons were still often encountered. The organization of nociceptive neurons in area 1 may be analogous to the segregation of rapidly and slowly adapting neurons in area 3b (Sur et al. 1984). Rapidly adapting neurons were found in all cortical layers but cells with slowly adapting responses were found only in the middle layers. The pattern of distribution of slowly adapting mechanoreceptive neurons suggested that there were bands or clusters of such neurons oriented in a rostrocaudal direction within the middle cortical layers. Nociceptive neurons in the middle cortical layers may be distributed in a similar way, although more experiments are needed to test this hypothesis. These data further suggest that modality-pure columns of nociceptive neurons do not exist. Such neurons were not found in layer VI and nociceptive neurons were intermingled with low-threshold cells having receptive fields in matching locations. This conclusion does not agree with the findings of Matsumoto et al. (1989). Based on peripheral and pulpal receptive fields, and response latencies to electrical stimulation, they concluded that tooth pulp-driven neurons were arranged in vertical columns in cat SI cortex.

Our results differ from those of Tommerdahl et al. (1996). They found that 52°C noxious thermal stimulus produced changes in blood flow confined to area 3a. Decreases in blood flow were found in areas 3b and 1. They also attempted to record from single nociceptive neurons in area 3a. Four neurons were identified that appeared to respond to 52°C noxious thermal stimulus. The authors did not identify the receptive field properties of these neurons, nor were the neurons tested for their ability to encode either noxious mechanical or noxious thermal stimuli. In addition, there was no attempt to control for the fact that noxious thermal stimulation produces arousal responses in many nociceptive SI neurons (Chudler 1988; Kenshalo and Isensee 1983). The lack of changes in blood flow in area 1 may be explained by a few observations. The most logical explanation may be that the optical imaging techniques used by Tommerdahl et al. are not sensitive enough to detect blood flow changes in area 1. A less plausible explanation may be that the processing of cortical nociceptive information in the owl monkey and the macaque differ substantially. We did not

routinely search area 3a in the present study. In past studies (Chudler et al. 1990; Kenshalo and Isensee 1983; Kenshalo et al. 1988), we routinely searched areas 3a and 3b, but did encounter neurons that encoded the intensity of noxious thermal stimulation.

Nociceptive neurons appear to be organized in vertically oriented aggregations or clumps. These aggregations do not appear to be evenly distributed across area 1. However, once a nociceptive neuron is located an average of 2.8 additional nociceptive neurons and 3.3 LTM neurons were found in the electrode track. These data suggest there is an almost equal probability that the next neuron isolated will be an LTM or nociceptive neuron. It is also apparent within an aggregation; the receptive fields of the nociceptive neurons are not identical but may shift with small movements of the electrode.

In the present series of experiments, NS neurons were located in the anterior half of the distribution of nociceptive neurons, whereas WDR neurons were distributed over a wider area of the somatosensory cortex. Given that NS neurons receive less submodality convergence than WDR cells, the lack of NS cells recorded in the posterior areas of SI is in general agreement with the observations of Iwamura et al. (1983a,b). They suggested that the amount of submodality convergence in low-threshold neurons is greater in more caudal areas of the cortex.

A number of differences are evident between the response characteristics of nociceptive neurons found in the monkey and those found in the rat. Lamour et al. (1983b) also found that neurons responsive to noxious stimuli in rat somatosensory cortex were intermingled with neurons responsive to innocuous stimuli. However, in their study nociceptive neurons were primarily located in layers V and VI. NS neurons were found almost exclusively in layers Vb and VI, while the majority of WDR neurons were found in layer V and only a few were located in layer VI. By contrast, the majority of nociceptive neurons in the macaques were located in the middle layers of SI. Other differences exist in the receptive fields of nociceptive neuron between the macaques and rats. For instance, the receptive fields of NS neurons in the rat often covered large areas of the body surface (Lamour et al. 1983a). In contrast, we found in monkeys that WDR neurons usually had larger receptive fields than NS neurons. The observations of Lamour et al. (1983a) are different from ours in the macaque and suggest that there are considerable species differences in the organization of nociceptive neurons in SI.

In summary, many of the differences between NS and WDR neurons found in the spinal and medullary dorsal horns are maintained at the level of the primary somatosensory cortex. Furthermore, there appears to be a spatial segregation of NS neurons in the anterior distribution of nociceptive neurons, whereas WDR neurons distributed over a much wider area of the cortex.

We appreciate the helpful comments made by Drs. E. Chudler and R. Caudle.

Present address of D. A. Thomas: Division of Basic Research, National Institute on Drug Abuse, Rockville, MD 20892.

REFERENCES

ANDERSON SA, KELLER O, ROOS A, AND RYDENHAG B. Cortical projection of tooth pulp afferents in the cat. In: *Pain in the Trigeminal Region*, edited by Anderson DJ and Matthews B. Amsterdam: Elsevier, 1977, p. 355–364.

ARMSTRONG-JAMES M AND GEORGE MJ. Influence of anesthesia on spontaneous activity and receptive field size of single units in rat SmI neocortex. *Exp Neurol* 99: 369–387, 1988.

BECK PW, HANDWERKER HO, AND ZIMMERMAN M. Nervous outflow from the cat's foot during noxious radiant heat stimulation. *Brain Res* 67: 373–386, 1974.

BEITEL R AND DUBNER R. Responses of unmyelinated (C) polymodal nociceptors to mechanical and thermal stimuli applied to monkey's face. *J Neurophysiol* 39: 1160–1175, 1976.

BESSOU P AND PERL ER. Responses of cutaneous sensory units with unmyelinated fibers to noxious stimuli. *J Neurophysiol* 32: 1025–1043, 1969.

BIEDENBACH MA, VAN HASSEL HJ, AND BROWN AC. Tooth pulp-driven neurons in somatosensory cortex of the primate including a review of the literature. *Pain* 7: 31–50, 1979.

BRINKMAN J, COLEBATCH JG, PORTER R, AND YORK D. Responses of precentral cells during cooling of post-central cortex in conscious monkeys. *J Physiol (Lond)* 368: 611–625, 1985.

BUSHNELL MC AND DUNCAN GH. Mechanical response properties of ventroposterior medial thalamic neurons in the alert monkey. *Exp Brain Res* 67: 603–614, 1987.

BUSHNELL MC, DUNCAN GH, DUBNER R, AND HE LF. Activity of trigeminothalamic neurons in medullary dorsal horn of awake monkeys trained in a thermal discrimination task. *J Neurophysiol* 52: 170–187, 1984.

CAMPBELL JN, MEYER RA, AND LAMOTTE RH. Sensitization of myelinated nociceptive afferents that innervate monkey hand. *J Neurophysiol* 42: 1669–1679, 1979.

CERVERO F, HANDWERKER HO, AND LAIRD JMA. Prolonged noxious mechanical stimulation of the rat's tail: responses and encoding properties of dorsal horn neurons. *J Physiol (Lond)* 404: 419–436, 1988.

CHAPIN JK, WATERHOUSE BD, AND WOODWARD DJ. Differences in the cutaneous sensory response of single somatosensory cortical neurons in awake and halothane anesthetized rats. *Brain Res Bull* 6: 63–70, 1981.

CHUDLER EH, ANTON F, DUBNER R, AND KENSHALO DR JR. Responses of nociceptive SI neurons in monkeys and pain sensation in humans elicited by noxious thermal stimulation: effect of interstimulus interval. *J Neurophysiol* 63: 559–569, 1990.

CROZE S, DULCAUX R, AND KENSHALO DR SR. The thermal sensitivity of polymodal nociceptors in the monkey. *J Physiol (Lond)* 263: 539–562, 1976.

DEJERINE J AND MOUZON J. Un nouveau type de syndrome sensitif cortical observe dan un cas de monoplegie corticale dissociee. *Rev Neurol* 28: 1265–1271, 1915.

DUBNER R AND BENNETT GJ. Spinal and trigeminal mechanisms of nociception. *Ann Rev Neurosci* 6: 381–418, 1983.

DUBNER R, KENSHALO DR, MAIXNER W, BUSHNELL MC, AND OLIVERAS JL. The correlation of monkey medullary dorsal horn neuronal activity and the perceived intensity of noxious heat stimuli. *J Neurophysiol* 62: 450–459, 1989.

DUBNER R, PRICE DD, BEITEL RE, AND HU J. Peripheral correlates of behavior in monkey and human related to sensory-discriminative aspects of pain. In: *Pain and the Trigeminal Region*, edited by Anderson DJ and Matthews B. New York: Elsevier, 1977, p. 57–66.

DUCLAUX R AND KENSHALO DR SR. Response characteristics of cutaneous warm receptors in the monkey. *J Neurophysiol* 43: 1–15, 1980.

DUNCAN GH, DRYER DA, MCKENNA TM, AND WHITSEL BL. Dose- and time-dependent effects of ketamine on SI neurons with cutaneous receptive fields. *J Neurophysiol* 47: 677–699, 1982.

FOERSTER O. *Die Leitungsbahnen des Schmerzgefuhls und die Chirurgische Behandlung der Schmerustande*. Berlin: Urban and Schwarzenberg, 1927.

GEORGOPOULOS AP. Functional properties of primary afferent units probably related to pain mechanisms in primate glabrous skin. *J Neurophysiol* 39: 71–83, 1976.

HARDING GW, STOGSDILL RM, AND TOWE AL. Relative effects of pentobarbital and chloralose on the responsiveness of neurons in sensorimotor cerebral cortex of the domestic cat. *Neurosci* 4: 369–378, 1979.

HARDY JD, STOLWIJK JAA, AND HOFFMAN D. Pain following step increase in skin temperature. In: *The Skin Senses*, edited by Kenshalo DR. Springfield: Thomas, 1968, p. 444–457.

HARDY JD, WOLFF HG, AND GOODELL H. *Pain Sensation and Reactions*. New York: Hafner, 1952.

HEAD H. *Studies in Neurology*. London: Oxford, 1920, vol. 2.

HEAD H AND HOLMES G. Sensory disturbances from cerebral lesions. *Brain* 34: 102–254, 1911.

HENSEL H. Cutaneous thermoreceptors. In: *Handbook of Sensory Physiology. Somatosensory System*, edited by Iggo A. New York: Springer, 1973, vol. II, p. 79–110.

HENSEL H AND KENSHALO DR. Warm receptors in the nasal region of the cat. *J Physiol (Lond)* 204: 99–112, 1969.

HOFFMAN DS, DUBNER R, HAYES RL, AND MEDLIN TP. Neuronal activity in medullary dorsal horn of awake monkeys trained in a thermal discrimination task. I. Responses to innocuous and noxious thermal stimuli. *J Neurophysiol* 46: 409–427, 1981.

HOLMES G. Disorders of sensation produced by cortical lesions. *Brain* 50: 413–427, 1927.

IGGO A AND OGAWA H. Primate cutaneous thermal nociceptors. *J Physiol (Lond)* 216: 77p–78p, 1971.

IWAMURA Y, TANAKA M, SAKMOTO M, AND HIKOSAKA O. Functional subdivisions representing different finger regions in area 3 of the first somatosensory cortex of the conscious monkey. *Exp Brain Res* 51: 315–326, 1983a.

IWAMURA Y, TANAKA M, SAKAMOTO M, AND HIKOSAKA O. Converging patterns of finger representation and complex response properties of neurons in area 1 of the first somatosensory cortex of the conscious monkey. *Exp Brain Res* 51: 327–337, 1983b.

IWATA K, ITOGA H, MURAMATSU H, TODA K, AND SUMINO R. Responses of bradykinin sensitive tooth-pulp driven neurons in cat cerebral cortex. *Exp Brain Res* 66: 435–439, 1987.

IWATA K, TSUBOI Y, MURAMATSU H, AND SUMINO R. Distribution and response properties of cat SI neurons responsive to changes in tooth temperature. *J Neurophysiol* 64: 822–834, 1990.

JONES EG AND BURTON H. Areal differences in the laminar distribution of thalamic afferents in cortical fields of the insular, parietal and temporal regions of primates. *J Comp Neurol* 168: 197–248, 1976.

JONES EG, COULTER JD, AND HENDRY SCH. Intracortical connectivity of architectonic fields in somatic sensory, motor and parietal cortex of monkeys. *J Comp Neurol* 181: 291–348, 1978.

JONES EG, FRIEDMAN DP, AND HENDRY SCH. Thalamic basis of place- and modality-specific columns in monkey somatosensory cortex: a correlative anatomical and physiological study. *J Comp Neurol* 48: 545–568, 1982.

JONES EG, WISE SP, AND COULTER JD. Differential thalamic relationships of sensori-motor and parietal cortical fields in monkeys. *J Comp Neurol* 183: 833–882, 1979.

KENSHALO DR SR AND BERGEN DC. A device to measure cutaneous sensitivity in humans and subhuman species. *J Appl Physiol* 39: 1038–1040, 1975.

KENSHALO DR SR AND DUCLAUX R. Response characteristics of cutaneous cold receptors in the monkey. *J Neurophysiol* 40: 319–322, 1977.

KENSHALO DR JR, CHUDLER EH, ANTON F, AND DUBNER R. SI cortical nociceptive neurons participate in the encoding process by which monkeys perceive the intensity of noxious thermal stimulation. *Brain Res* 454: 378–382, 1988.

KENSHALO DR JR, GEISLER GJ, LEONARD RB, AND WILLIS WD. Responses of neurons in the primate ventral posterior lateral nucleus to noxious stimuli. *J Neurophysiol* 43: 1594–1614, 1980.

KENSHALO DR JR AND ISENSEE O. Responses of primate SI cortical neurons to noxious stimuli. *J Neurophysiol* 50: 1479–1496, 1983.

KENSHALO DR JR, LEONARD RB, CHUNG JM, AND WILLIS WD. Response of primate spinothalamic tract neurons to graded and to repeated noxious thermal stimuli. *J Neurophysiol* 42: 1370–1389, 1979.

KENSHALO DR JR, THOMAS DA, AND DUBNER R. Somatosensory cortical lesions change the monkeys' reaction to noxious stimulation (Abstract). *J Dent Res* 68: 897, 1989.

KENSHALO DR JR AND WILLIS WD JR. The role of the cerebral cortex in pain sensation. In: *Cerebral Cortex*, edited by Jones EG and Peters A. New York: Plenum, 1991, p. 151–212.

KUMAZAWA T AND PERL ER. Primate cutaneous sensory unit with unmyelinated(C) afferent fibers. *J Neurophysiol* 40: 1325–1338, 1977.

LAIRD JMA AND CERVERO F. A comparative study of the changes in receptive-field properties of multireceptive and nocireceptive rat dorsal horn neurons following noxious mechanical stimulation. *J Neurophysiol* 62: 854–863, 1989.

LAMOTTE RH. Intensive and temporal determinants of thermal pain. In: *Sensory Functions of the Skin in Humans*, edited by Kenshalo DR. New York: Plenum, 1979, p. 327–361.

LAMOTTE RH AND CAMPBELL JN. Comparison of responses of warm and nociceptive C-fiber afferents in monkey with human judgements of thermal pain. *J Neurophysiol* 41: 509–528, 1978.

LAMOUR Y, GUILBAUD G, AND WILLER JC. Rat somatosensory (SmI) cortex. I. Characteristics of neuronal responses to noxious stimulation and comparison with responses to non-noxious stimulation. *Exp Brain Res* 49: 35–45, 1983a.

LAMOUR Y, GUILBAUD G, AND WILLER JC. Rat somatosensory (SmI) cortex. II. Laminar and columnar organization of noxious and non-noxious inputs. *Exp Brain Res* 49: 46–54, 1983b.

MAIXNER W, BUSHNELL MC, DUBNER R, KENSHALO DR, AND OLIVERAS JL. Responses of monkey medullary dorsal horn neurons during the detection of noxious heat stimuli. *J Neurophysiol* 62: 437–449, 1989.

MARSHALL J. Sensory disturbances in cortical wounds with special reference to pain. *J Neurol Neurosurg Psychiatry* 14: 187–204, 1951.

MATSUMOTO N, SATO T, AND SUZUKI TA. Characteristics of the tooth pulp-driven neurons in a functional column of the cat's somatosensory cortex (SI). *Exp Brain Res* 74: 263–271, 1989.

MATSUMOTO N, SATO T, YAHATA F, AND SUZUKI TA. Physiological properties of tooth pulp-driven neurons in the first somatosensory cortex (SI) of the cat. *Pain* 31: 249–262, 1987.

MELZACK R AND CASEY KL. Sensory, motivational and central control determinants of pain. In: *The Skin Senses*, edited by Kenshalo DR. Springfield: Thomas, 1968, p. 423–438.

MEYER RA AND CAMPBELL JN. Myelinated nociceptive afferents account for the hyperalgesia that follows a burn to the hand. *Science* 213: 1527–1529, 1981.

PEELE TL. Acute and chronic parietal ablations in monkeys. *J Neurophysiol* 7: 269–286, 1944.

PENFIELD W AND BOLDRY E. Somatic, motor and sensory representation in the cerebral cortex of man as studied by electrical stimulation. *Brain* 60: 389–443, 1937.

PENFIELD W AND JASPER H. *Epilepsy and the Functional Anatomy of the Human Brain.* Boston: Little, Brown and Co., 1954.

PRICE DD AND DUBNER R. Neurons that subserve the sensory-discriminative aspects of pain. *Pain* 3: 307–338, 1977.

ROOS A, RYDENHAG B, AND ANDERSON S. Activity in cortical cells after stimulation of tooth pulp afferents in the cat: intracellular analysis. *Pain* 16: 49–60, 1983a.

ROOS A, RYDENHAG B, AND ANDERSON S. Activity in cortical cells after stimulation of tooth pulp afferents in the cat: extracellular analysis. *Pain* 16: 61–72, 1983b.

RUSSELL WR. Transient disturbances following gunshot wounds of the head. *Brain* 68: 79–97, 1945.

SUR M, WALL JT, AND KAAS JH. Modular distributions of neurons with slowly adapting responses in area 3b of somatosensory cortex in monkeys. *J Neurophysiol* 56: 328–250, 1984.

SWEET WH. Cerebral localization of pain. In: *New Perspectives in Cerebral Localization*, edited by Thompson RA and Green JR. New York: Raven, 1982, p. 205–242.

TOMMERDAHL M, DELEMOS CJ, VIERCK CJ, FAVOROV OV, AND WHITSEL BL. Anterior parietal cortical response to tactile and skin-heating stimuli applied to the same skin site. *J Neurophysiol* 75: 2662–2670, 1996.

WILLIS WD. *The Pain System. The Neural Basis of Nociceptive Transmission in the Mammalian Nervous System*. Basel: Karger, 1985.

WINER BJ. *Statistical Principles in Experimental Design.* New York: McGraw-Hill, 1971.